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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 640

[Docket No. 98N–0608]

Revision of Requirements Applicable to Albumin (Human), Plasma Protein Fraction (Human), and Immune Globulin (Human)

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations by removing, revising, or updating specific regulations applicable to blood derivative products to be more consistent with current practices and to remove unnecessary or outdated requirements. FDA is taking this action as part of the agency's ''Blood Initiative'' in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood products, including blood derivatives.

DATES: This rule is effective [*insert date 30 days after date of publication in the* **Federal Register**].

FOR FURTHER INFORMATION CONTACT: Nathaniel L. Geary, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of May 14, 1999 (64 FR 26282), FDA published a direct final rule to amend the biologics regulations in part 640 (21 CFR part 640) by removing, revising, or updating specific regulations applicable to blood derivative products to be more consistent with current

practices and to remove unnecessary or outdated requirements. FDA issued these amendments directly as a final rule because the agency believed they were noncontroversial and that there was little likelihood that there would be comments opposing the rule. In the **Federal Register** of May 14, 1999 (64 FR 26344), FDA published a companion proposed rule under FDA's usual procedures for notice and comment in the event the agency received any significant adverse comments to the direct final rule. FDA received three significant adverse comments during the comment period, and the agency has considered these comments in developing the final rule.

In the **Federal Register** of March 14, 2000 (65 FR 13678), FDA published a direct final rule with a confirmation in part and technical amendment. The document confirmed those provisions for which there were no adverse comments. This final rulemaking responds to those proposed provisions for which there were significant adverse comments.

II. Responses to Comments on the Proposed Rule

A. Proposed § 640.81(e)

The proposed changes to § 640.81(e) were: (1) The insertion of the word ''continuously,'' to clarify that the heating process shall be continuous for the time and at the temperature specified in the regulations and (2) the removal of an extraneous degree sign.

One comment did not object to the proposed changes to § 640.81(e), but it recommended deletion of the sentence that currently precedes the sentence for which the changes are proposed. That sentence reads: ''Heating of the final containers of Albumin (Human) shall begin within 24 hours after completion of filling.'' The comment also stated that the proposed rule should be broadened to allow for heat treatment to occur in bulk during the manufacturing process.

FDA disagrees with the comment. Even though the comment did not address the proposed rule, but rather the regulation as it currently exists, the agency has considered the comment and the arguments listed in support of the recommended deletion and/or broadening. The comment listed several potential advantages of heating in bulk over heating in the final containers. These

included better control and monitoring, obviation of the need for a water bath and the attendant potential microbial contamination of the product, and diminished leaching of contaminants from the containers. The comment noted that heating in bulk would allow the product to be filled in a post-viral-inactivation filling suite.

Despite these theoretical advantages, the agency does not find that they provide sufficient assurance of safety equal to or greater than that provided by the current process to warrant deleting this portion of the regulation. Furthermore, the agency is not aware that any of the disadvantages of the current process implied by the comment cannot be overcome by appropriate process validation and adherence to current good manufacturing practice.

Nothing in the current regulation or the proposed rule precludes heat treatment in bulk during the manufacturing process for Albumin (Human), provided that it is conducted according to current good manufacturing practice and described in an approved Biologics License Application (BLA). An applicant who wishes to include such a step in the manufacture of Albumin (Human) should describe it in a BLA or Biologics License Supplement that addresses such matters as validation of the process and demonstration that the treatment does not affect adversely the characteristics of the product, including its purity, safety, and stability.

However, the agency has concluded that heat treatment in bulk, even for 10 to 11 hours at $60_{\pm}0.5$ °C, does not permit the manufacturer to forgo heating Albumin (Human) in the final containers, as prescribed in § 640.81(e). This requirement is intended to minimize the occurrence of viral transmission by albumin-containing products (Ref. 1).

B. Proposed § 640.81(f)

The proposed changes to § 640.81(f) would clarify the acceptable amounts of stabilizers that must be present in Albumin (Human) and Plasma Protein Fraction (Human) to reflect the amounts of those stabilizers that are currently used in these products.

One comment objected to the proposed quantity of sodium caprylate per gram (/g) of protein and recommended that the range be increased to allow higher quantities of caprylate/g of protein or, alternatively, that the quantity of sodium caprylate not be specified in the regulation.

The rationale for this recommendation included: (1) Caprylate is a more effective stabilizer than is acetyltryptophanate, which is currently used as a stabilizer in conjunction with caprylate; (2) the denaturation temperature of albumin is increased as the quantity of caprylate/g of protein is increased; and (3) the additional quantity of caprylate infused will not be expected to have any adverse effect.

FDA does not agree with the comment. The agency agrees that caprylate is a more effective stabilizer of albumin than is acetyltryptophanate. The observation that 0.08 millimole sodium caprylate/g of protein stabilizes albumin nearly as effectively as 0.08 millimole sodium acetyltryptophanate plus 0.08 millimole sodium caprylate/g of protein (Refs. 2 and 3) was one of the reasons underlying the proposed rule. The agency also agrees that increasing the quantity of caprylate/g of protein increases the denaturation temperature of albumin. For the heat treatment required by § 640.81 during the processing of albumin, however, the important factor is the effectiveness of stabilization at 60 °C. Once the quantity of stabilizer is sufficient to assure that the temperature at which denaturation is initiated is significantly above 60 °C, further increase in the quantity of stabilizer would not be expected to enhance the stability of albumin at this temperature (Ref. 3). This expectation has been confirmed in practice. When albumin was heated for 10 hours at 60 °C, increasing the ratio of caprylate to protein resulted in progressively better stabilization up to a ratio of 0.08 millimole sodium caprylate/g of protein; above that, little or no further stabilization occurred (Ref. 3). Furthermore, when sodium caprylate was present at a ratio of 0.08 millimole/g of protein, albumin remained as stable during continued heating (up to 24 hours) at 60 °C as it was after 10 hours at this temperature (Ref. 3).

Numerous biological effects of caprylate have been reported. Even a nonexhaustive listing reveals a broad array, including: (1) Hypoglycemia (Refs. 4 to 6); (2) hyperventilation (Refs. 7

and 8); (3) narcotic action in various animal species (Refs. 6, 9, and 10); (4) increased oxygen consumption and decreased clearance of long-chain fatty acids by the liver (Refs. 11 and 12); (5) vasodilation (Ref. 13); (6) decreased muscle contractility (Refs. 14 to 6); (7) altered epithelial and membrane permeability (Refs. 17 and 18), including alteration of the blood-brain barrier (Refs. 19 and 20); (8) inhibition of platelet reactivity (Refs. 21 and 22); (9) increased release of insulin and enzymes from pancreatic cells (Refs. 23 to 26); (10) altered carbohydrate metabolism (Refs. 5, 15, and 27 to 30), including glucose production (Refs. 4, and 31 to 33); (11) increased catabolism of muscle proteins (Ref. 34), decreased incorporation of amino acids into protein (Ref. 35), and alterations in amino acid metabolism (Refs. 36 and 37); (12) decreased ammonia production and metabolism (Refs. 31 and 38); and (13) depressed synthesis of DNA (Deoxyribonucleic acid) and RNA (ribonucleic acid) (Refs. 39 to 41).

In view of this broad range of demonstrated effects, it is difficult to predict the outcome of increased caprylate infusion in different patients and different clinical settings. For this reason, the agency believes that the ratio of caprylate to protein should not be increased above that necessary to stabilize albumin.

Many factors contribute to the stability of albumin during heating. These include not only the stabilizers noted here but also the pH (Ref. 42) and the chloride content of the solution (Ref. 3). Moreover, the contributions of these factors to the stability of albumin appear to be additive (Ref. 3). Therefore, conditions can be chosen to maximize the stability of albumin without increasing the quantity of caprylate above that specified in the proposed rule.

C. Proposed § 640.102(e)

The proposed change to § 640.102(e) would delete "30 to" in § 640.102(e).

One comment on proposed § 640.102(e) raised no objection, but it objected to the wording of other parts of the paragraph. The comment recommended that the first sentence be amended with definitions to provide increased clarity. It stated that the second sentence, as worded in both the current regulation and the proposed rule, seems not to allow for heating of the product at

elevated temperature for the purpose of viral inactivation; and it recommended that it be amended to incorporate this possibility.

The agency agrees that the parts of the regulation noted in the comment, as well as others that were not included, could be clarified and improved. The agency believes that making such changes should be done as part of an overall revision of the regulation and is beyond the scope of this rulemaking. With regard to the comment about the second sentence, if an applicant believes that heating at elevated temperature would improve the safety of Immune Globulin (Human) without compromising its other characteristics, such as purity and stability, the applicant should describe the process in a BLA or Biologics License Supplement and submit it to the agency as a request for an alternative procedure under § 640.120.

FDA has considered all comments in response to the proposed rule and has determined that proposed § 640.81(e) and (f) and § 640.102(e) should be issued as a final rule.

III. Analysis of Impacts

A. Review under Executive Order 12866 and the Regulatory Flexibility Act and Unfunded Mandates Reform Act of 1995

FDA has examined the impacts of the final rule under Executive Order 12866 the Regulatory Flexibility Act (5 U.S.C. 601–612 (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and therefore is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small business entities. Because the final rule amendments have no compliance costs and do not result in any new requirements, the agency certifies that the final rule will not have a significant negative economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

The Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in expenditures by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more in any one year. Because this rule does not result in expenditures by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more in any one year, FDA concluded that the proposed regulation is consistent with the principles of the Unfunded Mandates Reform Act without the need for further analysis.

B. Environmental Impact

The agency has determined under 21 CFR 25.31(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. The Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

V. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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10. *American Journal of Gastroenterology*, 69:187–190, 1978.

11. *European Journal of Biochemistry*, 141:223–230, 1984.

12. *Proceedings of the Society for Experimental Biology and Medicine*, 167:36–39, 1981.

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14. *Biomedica Biochimica Acta*, 45:S45–S50, 1986.

15. *Biochimica et Biophysica Acta* 1093:125–134, 1991.

16. *Folia Medica*, 34:12–18, 1992.

17. *Pharmaceutical Research*, 8:1365–1371, 1991.

18. *Journal of Pharmaceutical Sciences*, 77:390–392, 1988.

19. *Pediatric Neurology*, 1:20–22, 1985.

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21. *Thrombosis Research*, 4:479–484, 1974.

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23. *Metabolism*, 16:482–484, 1967.

24. *American Journal of Physiology*, 234:E162–E167, 1978.

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26. *Journal of Comparative Physiology*, B 166:305–309, 1996.

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28. *Journal of Reproduction and Fertility*, 23:307–317, 1970.

29. *European Journal of Biochemistry*, 86:519–530, 1978.

30. *Archives of Biochemistry and Biophysics*, 309:254–260, 1994.

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33. *Comparative Biochemistry and Physiology*, B 91:339–344, 1988.

34. *Folia Medica*, 35:23–27, 1993.

35. *Experientia*, 34:232–233, 1978.

36. *European Journal of Biochemistry*, 97:389–394, 1979.

37. *Journal of Biological Chemistry*, 267:11208–11214, 1992.

38. *Journal of Pharmacology and Experimental Therapeutics*, 197:675–680, 1976.

39. *Hepatology*, 5:28–31, 1985.

40. *Journal of Biological Chemistry*, 267:14918–14927, 1992.

41. *Journal of Lipid Research*, 38:2548–2557, 1997.

42. *Vox Sanguinis*, 47:19–27, 1984.

List of Subjects in 21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 640 is amended as follows:

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

1. The authority citation for 21 CFR part 640 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

2. Section 640.81 is amended by revising the last sentence in paragraph (e) and by revising paragraph (f) to read as follows:

§ 640.81 Processing.

* * * * *

(e) *Heat treatment.* * * * Heat treatment shall be conducted so that the solution is heated continuously for not less than 10, or more than 11 hours, at an attained temperature of $60_{\pm}0.5$ °C.

(f) *Stabilizer.* Either $0.08_{\pm}0.016$ millimole sodium caprylate, or $0.08_{\pm}0.016$ millimole sodium acetyltryptophanate and $0.08_{\pm}0.016$ millimole sodium caprylate per gram of protein shall be present as a stabilizer(s). Calculations of the stabilizer concentration may employ the labeled value for the protein concentration of the product as referred to in § 640.84(d).

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3. Section 640.102 is amended by revising the last sentence of paragraph (e) to read as follows:

§ 640.102 Manufacture of Immune Globulin (Human).

* * * * *

(e) * * * At no time during processing shall the product be exposed to temperatures above 45 °C, and after sterilization the product shall not be exposed to temperatures above 32 °C for more than 72 hours.

Dated: 8/4/00
August 4, 2000

Margaret M. Dotzel,
Asscciate Commissioner for Policy.

[FR Doc. 00–???? Filed ??–??–00; 8:45 am]

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